REMARKS

Claims 79 - 88 and 105 - 108 are in the application.

Claims 89 and 97 - 104 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. The Examiner has acknowledged that the applicant timely traversed the restriction (election) requirement in the reply to the restriction requirement filed on September 29, 2009.

In response to applicant's traverse, the Examiner has reconsidered and made final the restriction requirement.

The claims have been amended to more particularly point out and distinctly claim applicant's invention. In particular, a few minor typographical errors in claim 94 have been corrected. The amended is fully supported by the application as filed, and introduces no new matter.

I. Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 83 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed, and reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner states that claim 83 recites the limitation, "derivative of ..." in reference to the instantly claimed compounds and their "derivatives." The Examiner further states that the applicant has not described the claimed genus of "derivatives" in a manner that would indicate they were in possession of the full scope of this genus, or even to describe what this genus is comprised of.

Regarding the requirement for adequate written description of chemical entities, the Examiner directs the applicant's attention MPEP §2163, and notes that *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Id.* at 1566. The Examiner further notes that the Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be

met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (*quoting Guidelines*, 66 Fed. Reg. at 1106 (*emphasis added*)). The Examiner acknowledges that although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general, citing *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the Examiner states that the claims are drawn to derivatives of acrylic acid or of acrylamide polymers, and that the claimed "derivatives of..." encompass any compound that contains the identical core as the instantly claimed compound, with a differing of substituents quoted for the identical purpose. The Examiner observes that applicant describes no "derivatives of..." in the specification. The Examiner further asserts that no derivatives are described adequately enough to allow one skilled in the art to ascertain that the applicant is in possession of the entire scope of the claimed genus. The Examiner further states that the applicant has not described this genus in a manner that would allow one skilled in the art to immediately envisage the compounds contemplated for use. The Examiner concludes that the claims lack adequate written description for the myriad of compounds embraced by the claimed "derivatives thereof."

The Examiner further states that the description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention, citing *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") The Examiner deems that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The Examiner's conclusion is not correct.

One of ordinary skill in the art would instantly understand what was meant by "derivatives of acrylic acid or of acrylamide polymers" in the context of the present disclosure. The basic chemistry relating to the reaction of acrylic acid with alcohols to form esters, with amines to form amides, etc. has been well known for over a hundred years, and the practice of referring to these well known compounds as "derivatives" is universal among chemists. Applicant appends a dictionary definition of "derivative" taken from Hackh's Chemical Dictionary, evidencing the use of "derivative" in the chemical arts.

The written description requirement does not require an applicant to expressly recite what is well-known in the art. The term "derivative" is well understood in the chemical arts. *See, for example, Ex parte Mahler*, Appeal 2009-012959 (BPAI December 27, 2010) (reversing lack of written description rejection; use of "derivative"). Moreover, an Examiner's rejection pursuant to Section 112, first paragraph, for lack of written description, based on the use of "acrylic acid derivative" has recently been considered, and reversed, by the Board. *Ex parte Bodmeier*, Appeal 2009-014588 (BPAI March 8, 2010).

Reconsideration and withdrawal of this rejection are respectfully requested for this reason.

II. Rejection of Claims 79 - 87, 90, 92 - 96 and 105 - 108 Under 35 U.S.C. 103(a)

Claims 79-87, 90, 92-96 and 105 - 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,503,955 ("Dobrozsi") and U.S. Patent 6,355,272 ("Caramella"). This rejection is also respectfully traversed, and reconsideration and withdrawal of the rejection are respectfully requested.

A. The Examiner's Rejection

The Examiner states that Dobrozsi teaches pourable liquid vehicles comprising a) 26% - 100% polyoxyalkylene block copolymer, b) 0-70% glycol and 0-50% water. Regarding claim 85, the Examiner observes that Dobrozsi's vehicles have a viscosity value of less than or equal to 7 pascal-seconds, which is equivalent to less than or equal to 7000 millipascals. Regarding claims 79, 83, 84, 86 and 108, the Examiner notes that Example XI demonstrates a composition comprising Promethazine HCL, an antihistamine antiemetic, which can be considered an active ingredient belonging to the

therapeutic class, in an amount of .25%. The Examiner further observes that Dobrozsi's composition further comprises Carbomer (a copolymer of acrylic acid, as defined by the instant specification and claims to be a liquid matrix ingredient of the inverted class) in amounts of 1.0%. Regarding claim 86, the Examiner notes that the active agent is milled to reduce its particle size, thus being in a solid state and is mixed with the poloxamer Pluronic L62, present in amounts of 98.75%, which can be considered an organic solvent. The Examiner states that the poloxamer has both a hydrophilic and a hydrophobic segment (citing col. 6, lines 8 - 9). Regarding claim 90, the Examiner states that although Dobrozsi does not specify if the active agent is a coated or uncoated powder, both are acceptable as recited by the instant claims. The Examiner concludes that the powder of Dobrozsi satisfies the instant claims, as one of skill in the art would recognize that a powder is either coated or uncoated. The Examiner further states that regarding claims 106 and 107, Example XIX demonstrates a pourable liquid vehicle of Dobrozsi which is filled into hard gelatin capsules or soft elastic gelatin capsules to provide controlled release of the active agent. Regarding claim 81, the Examiner states that after the gelatin capsule is swallowed, the shell dissolved in the gastrointestinal tract and the liquid fill immediately transforms into a slow dissolving gel that provides controlled release of the active agent.

The Examiner admits that Dobrozsi does not teach the at least one ingredient modulating the release of the active agent to be a polysaccharide as recited by instant claim 92-94, and that Dobrozsi also does not teach the limitations recited by instant claims 91 and 95-96.

However, that Examiner asserts that regarding claims 91 -- 94 and 96, Caramella teaches a complex between carrageenan and a water-soluble drug in powder form having an average particle size between 10 and 100 micrometers (citing the Abstract). The Examiner notes that this complex can be used to create controlled release pharmaceutical compositions, and that suitable water-soluble drugs include Promethazine HCL (citing col. 4, lines 18 - 19). The Examiner further asserts that regarding claim 95, Caramella's controlled release composition contains the complex in amounts ranging from 60-100%, and that Example 1 demonstrates a complex containing carrageenan (43.86%) and Promethazine HCL (56.14%), thus overlapping with the instantly claimed ranges. The Examiner asserts that the complex can be used in the preparation of solid oral dosage forms tablets, pellets and granules, and that said pellets

and granules can be contained in hard or soft capsules (citing col. 4, lines 57 - 61). The Examiner further notes that regarding claim 105, the employment of small particle size fractions reduces the release rate to values that are suitable for once a day administration, meaning a release completed within 20-24 hours (citing col. 4, lines 64 - 67 to col. 5, line 1).

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Dobrozsi and Caramella, since one of skill in the art would have been motivated to include the complex (carrageenan and an active agent, such as Promethazine HCL) into the pourable liquid vehicle of Dobrozsi, in order to create a capsule pharmaceutical composition suitable for once a day administration having a completed release between 20-24 hours. The Examiner asserts that one of skill in the art would expect reasonable success as both Dobrozsi and Caramella teaches controlled release pharmaceutical compositions, having an active agent in particle form, which can be in the form of soft or hard capsules.

Regarding claims 80 and 82, the Examiner asserts that as the combination of the prior art references teach all the structural limitations of the claims in amounts overlapping with those amounts instantly claimed, the composition taught by the prior art and the composition of the instant claims are expected to have the same properties, absent evidence to the contrary.

B. Applicant's Response

Applicant respectfully traverses that Examiner's conclusions, and contends that the cited references do not make a *prima facie* case of obviousness. The Examiner's conclusion in based on factual errors and the Examiner has not provided a reasoned, rational explanation for the rejection.

The present claims, and in particular, independent claim 79, require "at least one liquid matrix ingredient of the inverted latex class." Neither Dobrozsi nor Caramella disclose an inverted latex, and there is nothing in either Dobrozsi or Caramella individually nor in the combination of the two that would teach, suggest or disclose the use of an inverted latex in applicant's presently claimed invention to one of ordinary skill in the art. Further, the Examiner has not provided a reasoned explanation of how the suggested combination of Dobrozsi and Caramella, which

employ significantly different chemical techniques to accomplish controlled release of active ingredients, could be accomplished by one of ordinary skill in the art.

"Inverted latex" is a term well known in the chemical arts. For example, the term is used in U.S. Patents 3,724,547, 3,780,806, 3,998,727, 5,988,455, 6,197,287, 6,296,859, 6,346,239, 6,375,959, and 7,834,085. Dobrozsi's "pourable liquids" are not "invert latexes." Because the cited combination of references does not disclose, teach or suggest a required component of applicant's presently claimed compositions, no *prima facie* case has been established.

An "invert" or "inverted" latex is a liquid plastic polymer. It is obtained by polymerization of the monomer in a liquid medium containing different compounds. This polymerization is described in the specification of the present application (see, paragraphs [0045] - [0063]). The process of the polymerization and the products obtained from this synthesis are disclosed in a number of patents referenced in the specification (see, paragraphs [0064] - [0068]). Invert latexes can be synthesized by the polymerization of the monomer (e.g. acrylic acid or acrylamide, which give normally "plastic" polymers) in a mixture containing suitable surfactants, following by distillation to evaporate the water. During the formation of the polymer, the polymer becomes entrapped in its surfactants giving a "liquid" instead of a solid plastic polymer. The presently claimed invention does not include a polymerization step, but rather employs the product of the liquid polymerization, the invert latex, as a matrix-forming agent to slow down the release of an active ingredient due to the fact that the tensioactive entrapped in the polymer maintains its capacity to gel the polymer itself. The invert latex itself has no tensioactive properties like the poloxamers described in Dobrozsi's patent.

Dobrozsi's aim is to realize moistening surface products, not sustained release gelled products in uniform soft or hard capsules. Moreover, the mechanism of gelling is temperature dependent, unlike the presently claimed invention, and the ingredients used by Dobrozsi to obtain this effect are tensioactives and not polymers, two chemical identities being totally different.

As explained in the context of applicant's traverse of the Examiner's restriction requirement, Dobrozsi describes "pourable liquids" for moistening surfaces and aqueous environments, and that these "pourable liquids" contain water from 1% to 50%.

However, in the presently claimed invention, no water is added to the invert latex due to the fact that the mixtures developed with this new ingredient have to be filled

in soft and hard capsules. One of ordinary skill in the art would understand that the "pourable liquids" of Dobrozsi could not be used for filling capsules since the water would tend to dissolve the capsule walls, rendering the capsules unusable for their intended purpose.

Further, the specific "liquid matrix ingredients" disclosed by Dobrozsi are polyoxyalkylene block copolymer, ethylene oxide and propylene oxide copolymer. These polymers are not presently claimed.

The purpose of the presently claimed invention is not to moisten surfaces but to release slowly active substances in the gastro intestinal tract. Nothing in Dobrozsi speaks about or suggests the sustained release of active ingredients. Moreover, nothing in Dobrozsi discloses or suggests that monobasic and dibasic phosphate act like a release modulator. This is simply the Examiner's assumption, and the Examiner has not provided any factual basis or reasoned explanation for this assumption.

One of ordinary skill in the art would understand that the monobasic and dibasic phosphates are simply buffer ingredients to keep the pH of the "pourable liquid" around pH 7 for a nasal application. Any person skilled in the art knows that the pH of nasal solutions must be around 7.

Therefore, Dobrozsi does not disclose or suggest the presently claimed invention.

Caramella does not remedy this omission, in that there is no disclosure of a release modulator in Caramella. Therefore, there is nothing in the combination of Dobrozsi and Caramella, nor in either of them considered individually would teach, suggest or motivate one of ordinary skill in the art applicant's presently claimed invention.

Caramella discloses a complex formed between carrageenan and a water soluble active ingredient by adding water. This mixture is dried and then milled. The powder obtained from this process is transformed to a dry form: tablets, pellets or granules. These two latter products can be filled in hard capsules or soft capsules (col. 4, line 56 - 61). Therefore, the Caramella's goals are differ from those of the presently claimed invention.

Caramella uses carrageenan as a sustained release ingredient, and not a synthetic polymer as acrylate or acrylamide polymers. Carrageenans are disclosed in the present specification for use in preparing soft capsule shells, as a substitute for

gelatin in soft capsules, but not as a sustained release ingredient. As employed by Caramella, carrageenan will not slowly release an active ingredient from the soft capsule (see, U.S. Patent 6,331,205). Caramella's complex of carrageenan and water soluble drug is a powder. By comparison, the invert latex employed in the present invention is a liquid polymer. Caramella's sustained release form is a solid form, namely, tablets, granules or pellets, and not a liquid form as is presently employed. Indeed pellets or granules can be put in hard or soft capsules, but in this case it is under powder form and not under a pellets or granules suspension filled in a capsule. Caramella states that the controlled release pharmaceutical compositions preferably take the form of tablets (col. 4, lines 62 - 64).

With respect to the dependent claims:

Regarding claim 85, the Examiner observes that Dobrozsi's vehicles have a viscosity value of less than or equal to 7000 millipascals. However, just because Dobrozsi discloses an overlapping range of viscosity does not mean that Dobrozsi's compositions perform in the same way as applicant's presently claimed compositions. As emphasized above, Dobrozsi does not disclose inverted latexes.

As an example, high concentration solutions of hydroxypropylmethylcellulose can exhibit viscosities in the range disclose by Dobrozsi. But these solutions can't be filled in soft capsules due to the water as solvent of these solutions. Even if it was the case, these solutions are not going to gel in contact with water or biological fluids.

It should also be noted that Dobrozsi's compositions are defined in term of their "T value," which must be greater than or equal to about 1.3 (col. 18, lines 9 - 15). Dobrozsi ties η_f to T value. This last parameter determines the tendency of Dobrozsi's vehicles to gel at a temperature of 37°C: $T = \eta_0 / \eta_f$ where η_f is the viscosity of the vehicle at 25°C and η_0 the viscosity of the vehicle after dilution in water at 37°C. Dobrozsi' mechanism is totally different than that of the presently claimed invention due to the fact that the matrix formation, gelling mechanism, is totally independent to the body temperature and the viscosity of the liquid compositions. Indeed, surprisingly even for a low viscosity of the liquid compositions, 50 millipascals, the process of instantaneous gelling still occurs immediately after the opening of the capsule, due to the invert latex properties containing in these liquid compositions. There is no need of temperature and of water concentration, just a simple contact with the biological fluids.

Regarding claims 79, 83-84, 86 and 108, the Examiner states that Dobrozsi's Example XI comprises Carbomer®, a copolymer of acrylic acid, "as defined" by the instant specification and claims to be a liquid matrix ingredient of the inverted class, in amounts of 1.0%. This is not correct. The present specification does not define "liquid matrix ingredient of the inverted latex class" in terms of chemical composition alone, but rather in terms of the structure or morphology of the composition (i.e. "inverted latex'). Thus, while it may be possible for the Carbomer of Example XI to be processed in some why to provide an inverted latex, Dobrozsi in Example XI does not disclose the Carbomer in that form, and consequently the limitations of claims 79, 83-84, 86, or 108 cannot be and are not met by this disclosure.

It should be noted that the solvents used to dissolve these materials are organic solvents; oils (vegetable, mineral, natural) or solvents. The poloxamers used in Dobrozsi are a tensioactive. No tensioactive has been mentioned to dissolve the plastic polymer under powder form by the present specification. Even if Dobrozsi discloses Carbomer, mixed with 98.75% of poloxamers, the gelation process will be provided by the poloxamers only and not by 1% of Carbomer. Moreover, mixing the tensioactive with Carbomer which is a plastic polymer under a powder form, is not going to give the same result as invert latex (liquid polymer) because in one case the polymer is dispersed in the tensioactive (Carbomer and tensioactive) and in the second case the tensioactive is entrapped in the polymer net (invert latex). Likewise, to obtain a gelation of the Carbomer it is necessary to neutralize the solution with a solution of sodium hydroxide or any kind of alkaline solutions. In example XI, there is no alkaline ingredient and the pH of poloxamers like Pluronic L62 is between 5 and 7.5, which is not enough to neutralize Carbomer.

Regarding claim 86, the Examiner notes that the active agent is milled to reduce its particle size, and in a solid state and is mixed with the poloxamer Pluronic L62, present in amounts of 98.75%, which can be considered an organic solvent.

However, the Examiner does not provide any evidence for her statement that Pluronic L62, a surfactant, can be "considered" to be an organic solvent. Pluronic L62 is a liquid surfactant. The solvents referenced in the present application are organic solvents, just organic liquids having solubilization properties like water. They are used to dissolve active ingredients insoluble in water. Indeed vegetable oils, minerals oils, natural oils, synthetic oils, ethanol, propanol, etc. have never been considered in the

chemical arts to be surfactants, just solvents. Oils simply have never had a hydrophilic and a hydrophobic segment, nor does ethanol or any of the alcohols which can be used for pharmaceutical application.

I Claim 86 does not reference an active agent as being milled, but instead merely relates to active ingredients belonging to therapeutic classes. There is nothing in the disclosure relating to milling, although the specification discloses that the active ingredients can be incorporated in the invert latex in a powder form having a granulometric distribution size ranging from 1 µm to 1000 µm (paragraphs [0103] and [0104]).

The Examiner's comment in this instance appear to be intended to address claim 88, rather than claim 86, which relates to dissolving or dispersing the active ingredient in oils or organic solvent having a lipophilic, hydrophilic or hydrolipophilic nature. This means that the solvent used for the solubilization of the active could be lipophilic if the active is insoluble in water, or hydrophilic if the active is soluble in water, or hydrolipophilic if the active can be solubilized in both, water and organic solvent. For the dispersion of the active ingredient, the process is similar, but in an opposite manner: hydrophilic solvent for active insoluble in water, lipophilic solvent for an active insoluble in organic solvent (cf. paragraphs [0083] and [0107]).

Regarding claim 90, the Examiner asserts that Dobrozsi's powder would satisfy the limitations of this claim, because one of skill in the art would recognize that the active ingredient could be either a coated or uncoated powder. However, nothing in Dobrozsi relates to coated or uncoated particles of active substances. To speak about coated or uncoated particles suggests that the mechanism of active ingredient release from a support is well understood, which does not seem to be the case of Dobrozsi because no dissolution profiles are given. In contrast, in the present application the slow release mechanism through the matrixes is evidenced by the dissolution profiles of ibuprofen. Depending of invert latex used, the rate of release of ibuprofen varies. Ibuprofen is dispersed in powder form in the invert latex to decrease the rate of release. If a liquid form of ibuprofen were used, such as an alcoholic solution, there would be an acceleration of Ibuprofen release. If it were desired to slow down the rate of ibuprofen release, a coated form of ibuprofen particles could be employed.

Regarding dependent claims 106 and 107, the Examiner has noted that Dobrozsi's Example XIX demonstrates a pourable liquid vehicle which is filled into hard

gelatin capsules or soft elastic gelatin capsules to provide controlled release of the active agent. Nevertheless, Dobrozsi employs pourable liquid vehicles to deliver compositions, materials and substances to moistened surfaces and aqueous environments. Capsules are dosage units, not "pourable liquids," and these dosage units, even if there is a liquid inside, are going to deliver its content in the stomach without moistening the surface of the stomach. Dobrozsi does not provide dissolution profiles for such capsules to show that the rate of release of the active ingredient is reduced by the formulation developed by Dobrozsi. If even it this were true, that Dobrozsi's formulations decrease the release of active ingredients, the matricial agents are not the same and the mechanisms to obtain the matrix are totally different. Dobrozsi uses surfactants to swell and gel the components when body temperature is achieved. In contrast, the present invention uses an invert latex (liquid plastic polymer) to gel instantaneously independently of the temperature.

As to claims 91 - 94 and 96, the Examiner notes that Caramella teaches a complex between carrageenan and a water-soluble drug in powder form having an average particle size between 10 and 100 micrometers. However, in Caramella a mixture of carrageenan and the water-soluble drug is dried and then milled to obtain an appropriate particle size to optimizer the sustained release of the active ingredient. However, the present application discloses that carrageenan is employed as an ingredient to reinforce the structure of the matrix formed instantaneously just after the opening of the capsule. In this case, the carrageenan is not combined with the active ingredient, but rather is dispersed in solid form in the invert latex. No complexation occurs inside the capsule between the active ingredient and carrageenan. Moreover, the first step of Caramella's process is dissolution in water. Even if Caramella's mixture obtained at the first step of the process is liquid or pasty, it is impossible to fill soft or hard capsule with this mixture because the shells are going to be dissolve in water of the mixture. The present application discloses the use of carrageenan twice. First, the use of carrageenan is disclosed not as the content of the capsule, but rather as the shell of the capsule. In this case carrageenan is a substitute for gelatin. Such soft capsules are available commercially under the name of Vegicaps®. Second, the present application discloses the use of carrageenan as an ingredient to reinforce the structure of the matrix formed instantaneously just after the opening of the capsule. In this case the carrageenan is not combined with the active, and is dispersed in solid form in the invert

latex where there is no water. Moreover, the first step of Caramella's process is a dissolution using water. Even if the Caramella's mixture obtained at the first step of the process is liquid or pasty, it is impossible to fill soft or hard capsule with this mixture because the shells are going to be dissolve with water, solvent of the mixture.

Regarding claim 95, the Examiner contends that Caramella's controlled release composition contains the complex in amounts ranging from 60 - 100%, and that Example 1 demonstrates a complex containing carrageenan (43.86%) and Promethazine HCL (56.14%), thus overlapping with the instantly claimed ranges. This is not correct, because Caramella does not disclose any ingredients modulating the release of the active ingredient from the carrageenan complex. Caramella's carrageenan complex plays the same role as the invert latex in the present application and Dobrozsi's poloxamers. In the present invention, carrageenan can be used as a hydrophilic additive, but is not combined with anything as in Caramella.

The Examiner has also asserted that Caramella's complex can be used in the preparation of solid oral dosage forms tablets, pellets and granules, and that said pellets and granules can be contained in hard or soft capsules. Of course, granules or pellets can be used to fill hard capsules. But in this case no solvent is required to fill the capsules, the dry powder itself is enough. In this case, sustained release is obtained by the opening of the capsule in the stomach or intestine and the pellets or granules are individually dispersed in the biological fluids and release slowly its content. For filing soft capsules, it is well known in the art that generally a solvent is required. But Caramella does not disclose solvents. Therefore, it is impossible to say if such solvents were to be used, they would delay or increase the rate of release. Again, Caramella's compositions differ fundamentally from those of the present invention. Caramella discloses a sustained release system based on complexation between carrageenan and a water soluble ingredient. In the present invention, the active ingredient is dispersed in an invert latex.

Regarding claim 105, the Examiner notes that the use of small particle size fractions reduces the release rate to values that are suitable for once a day administration. However, it is well known in the art that any practical sustained release form must release its active ingredient in more than 8 hours, and with a maximum of 24 hours. What is important is not the period of release, but rather the manner in which the release is achieved. In the present invention, an inverted latex is employed for attaining

a release of an active ingredient over a sustained period, such as within 8 hours. Caramella employs a carrageenan complex with a water soluble drug. Dobrozsi uses poloxamers as sustained release support to achieve not "a once a day" administration but "a threefold" a day (col. 17, lines 40 - 43).

The Examiner's conclusion that it would have been prima facie obvious to combine the teachings of Dobrozsi and Caramella is not correct. The Examiner's explanation of the motivation of one of ordinary skill in the art is not reasonable. While both disclose controlled release pharmaceutical compositions, the two employ entirely different mechanisms for achieving control of the release of the active ingredient. The Examiner has not explained how one of ordinary skill in the art could possibly anticipate what would happen if the two were combined as suggested by the Examiner. Merely adding Caramella's complex to the pourable liquid of Dobrozsi could destroy the controlled release entirely, or have entirely unanticipated results.

Further, regarding claims 80 and 82, the Examiner has incorrectly asserted that as the combination of the prior art references teach all the structural limitations of the claims in amounts overlapping with those amounts presently claimed.

Claim 80 requires an Inverted latex. This is a structural limitation which is not taught, suggested, or disclosed in either Dobrozsi or Caramella or in the combination of the two. The present application does not disclose any other components as providing a sustained release matrix instantaneously.

As noted above, while other components such as carrageenan are disclosed, they are employed as "modulating agents" similar to Caramella (column 4, lines 50 - 56). For example, Caramella discloses carrageenan and water soluble drug complex as the sustained release system, in a powder form, and hydroxypropylmethylcellulose (HPMC) added to the tablets as modulator of the drug release. In the present application, an invert latex is disclosed as the sustained release system, in a liquid form, and modulators of the release dispersed in the sustained release system. Therefore, even if the same modulating agents were disclosed in Caramella and the present application, patent, they are not used in the same way. One is used in solid form (Caramella) and the other is used in liquid form (the present application). One skilled in the art would understand that an ingredient used in a different physical is not going to provide the same result. One of ordinary skill in the art would understand that in Caramella the HPMC is going to form a viscous gangue around a solid core, while in the present

invention the HPMC particles are going to swell individually inside a viscous gangue (or matrix) formed by the invert latex.

Claim 82 relates to the time required for the invert latex to gel. Nothing in Dobrozsi indicates the time required for gelation. No time is given to achieve this transformation (cf. col. 1, lines 13 - 16). Since this transformation depends on the temperature, the time needed to transform the pourable liquid to gel must be broad and variable. When applied to skin the transformation of this liquid will be long due to the equilibrium needed between skin temperature (37°C) and the air (19 - 20°C). In contrast, the present application defines the terms "instantaneous" or "rapidly" (paragraph [0040]). As the mechanism of the matrix formation is totally different, it is not possible to compare the time for formation of the matrix of Dobrozsi with that of the presently claimed invention. In the present application, the time frame is determined by the action of water to provide the gel formation. With water, no gel is formed. In Dobrozsi, no time frame is given because it is temperature the most important parameter for the matrix formation. While water may be present, it is does not determine the rate of matrix formation.

Reconsideration and withdrawal of the rejection under Section 103(a) over Dobrozsi and Caramella is respectfully requested for these reasons.

III. Rejection of Claim 107 Under 35 U.S.C. 103(a)

Claim 107 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrozsi and Caramella as applied to claims 79-87, 90, 92-96 and 105-108, and further in view of *Int. Journal of Pharmaceutics*, Vol. 231, January 2002, pages 83- 95 ("Cole"). This rejection is also respectfully traversed, and reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner states that Dobrozsi and Caramella teach all the limitations of instant claims 79-87, 90, 92¬96 and 105-108, but do not teach the capsule to be made of hydroxypropylmethylcellulose (HPMC), as elected. The Examiner further states that Cole teaches enteric coated HPMC capsules designed to achieve intestinal targeting, which provide a good adhesion, which facilitates coating the capsules with enteric polymer coatings (citing the abstract). The Examiner notes that the most commonly used material for manufacturing capsules is gelatin. The Examiner states that although it is possible to coat hard gelatin capsules, the process is at best very sensitive,

especially if an aqueous coating system is used, and can lead to shell embrittlement and poor adhesion of the coat to the smooth gelatin surface. The Examiner further states that a pre-coating can reduce interactions between the gelatin and the enteric polymer but is time consuming and complicated. The Examiner notes that HPMC capsules have been available commercially, mainly to the dietary supplement industry as a vegetarian alternative to gelatin, for approximately 10 years. The Examiner further notes that as HPMC is often used as a pre-coating material for enteric coated tablets, it may be expected that the application of enteric type polymers to a capsule made from HPMC would result in 'good polymer to polymer' adhesion and compatibility (citing page 85). The Examiner also states that a procedure recommended for coating gelatin capsules also involved pre-coating with Eudragit® L 30 D-55 plasticized with glycerol to improve adhesion and storage stability. The Examiner states that when the capsule itself is made of a cellulose derivative it would be expected, based on the experience with enteric coating of tablets with a pre-coating of HPMC, that a pre-coating step could be eliminated. The Examiner states that gelatin capsules have a very glossy surface due to the fact that the amount of regular reflection from the surface is high and the amount of diffuse reflection is low. The Examiner further notes that, in contrast, HPMC capsules have a visually matt surface with a greater amount of diffuse reflection, suggesting a more irregular surface. The Examiner states that during the coating process the temperature of the capsule bed reaches 25-27 °C, and at this temperature HPMC is soluble and will start to dissolve in the aqueous based film providing a strongly adhesive surface. The Examiner further notes that gelatin, on the other hand, is only slightly soluble at this temperature and its surface characteristics will remain virtually unchanged (citing page 87). The Examiner also notes that enteric coated HPMC capsules can thus be considered to provide a good container for drugs during the early development phase providing the possibility of drug release either in the small intestine or towards the colon (citing page 94).

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Dobrozsi/Caramella and Cole. The Examiner asserts that based on the teachings of Cole one of skill in the art would have recognized that the material, with which the capsule of Dobrozsi was made, could be changed depending on the type of pharmaceutical composition desired. The Examiner further states that one of skill in the

art would recognize that HPMC capsules have certain advantages over gelatin capsules for use in pharmaceutical capsules having an enteric polymer coating, due to enhanced adhesion and are prepared in a simpler, easier way. The Examiner also concludes that one of skill in the art would have a reasonable expectation of success absent evidence to the contrary.

Applicant respectfully contends that the cited combination of references does not make out a *prima facie* case of obviousness because an element of the independent claim from which claim 107 depends is lacking, namely, an ingredient modulating the release of the active ingredient from the matrix formed *in situ*.

This dependent claim, and all other dependent claims, depends directly or indirectly from amended claim 79, and thus simply add further limitations to the subject matter of claim 79. However, as argued above, claim 79 as amended is patentable over the art of record. Since the independent claim is not obvious over the cited art, the dependent claims including further limitations must also be patentable over the cited art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1696 (Fed. Cir. 1988).

Claim 107 simply relates to the types of capsules which can be filled with the compositions of the present invention, namely, hard capsules, and soft capsules which the shell of thereof are made with gelatin, carrageenan, starches, HPMC, polyvinylic alcohol derivatives.

Caramella similarly discloses the delivery vehicles for her granules or pellets, such as hard and soft capsules, and how her granules can be transformed into tablets suspensions, etc. The same is true for Dobrozsi's formulations. These can be delivered as syrups, topical creams, nasal sprays, suppositories, or soft capsules.

Independent claim 79 from which claim 107 depends requires an inverted latex in liquid form which gives a matrix by instantaneous gelation on contact with body fluids, where Caramella discloses a carrageenan complex with water soluble drugs under powder form and Dobrozsi discloses poloxamers in a liquid giving a gel induced by a increase in temperature.

Cole discloses enteric capsules. However, one of ordinary skill in the art would understand that enteric capsules are not sustained release capsules but rather provided a delayed release, as is apparent from the title of the Cole's publication. An enteric capsule is a capsule having a shell which resists to gastric juice (acid pH). In intestine, where the pH is around 5.00 to 7.50, the shell dissolves immediately releasing its

contents in the intestine, without sustaining the release. The capsules, in this case, are hard capsules, are coated with a polymer, Eudragit, which is known as a methacrylic resin in powder form before being dissolved in organic solvent and sprayed onto the capsules. Therefore, Cole fails to disclose sustained release, but rather employs a polymer in powder form which is dissolved before being sprayed onto the capsules. The shells of capsules are also made with HPMC. Thus, there is no relationship whatsoever between Cole and the presently claimed invention, which employs HPMC for modulating the release from the content of the capsule, and not for the manufacturing of the shell.

Reconsideration and withdrawal of this rejection are respectfully requested for these reasons.